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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/265,191	CARSON ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *202-206* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *202-206* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/9/02 has been entered.

Claims 202-206 are pending in the present application, and they are examined on the merits herein.

Response to Applicants' amendment

The rejection of claim 206 under 35 U.S.C. 103(a) as being unpatentable over Felgner et al. (U.S. Patent No. 6,214,804) is withdrawn.

The rejection of claim 203 35 U.S.C. 103(a) as being unpatentable over Krieg et al. (U.S. Patent No. 6,194,388 with the effective filing date of July 15, 1994: IDS) in view of Davis (U.S. Patent No. 5,780,448 with the effective filing date of November 07, 1995) or Applicants' admission of record (Amendment C filed 10/31/01 in Paper No. 28, page 8, second last paragraph and page 9, second paragraph) is withdrawn.

Priority

The present application is a continuation of U.S. Serial No. 08/593554, filed January 30, 1996, now abandoned, which is a continuation-in-part of U.S. Serial No. 08/446,691, filed June 7, 1995, now abandoned, which is a 371 national phase filing of PCT/US94/09661, filed August 25, 1994, which designated the U.S., which is a continuation-in-part of U.S. Serial No. 08/112,440, filed August 26, 1993.

Upon review of the specifications of great-grandparent (U.S Serial No. 08/112,440), grandparent (U.S. Serial No. 08/446,691) and parent (U.S. Serial No. 08/593,554) applications and comparison with the specification of the present application, it is determined that the pending claims are only entitled to the priority benefit of the filing date of January 30, 1996. When read in light of the present specification, claims 202 and 203 encompass a composition comprising a recombinant antigen and any plasmid including an immunostimulatory nucleic acid sequence comprising AACGTT, wherein C is unmethylated, and wherein the immunostimulatory nucleic acid sequence is either already present in the plasmid or it is inserted into the plasmid in any desired copy numbers, including the plasmid pREP7 (see instant specification, page 11, second full paragraph, last paragraph continues to first paragraph on page 12), and that said antigen is produced by a process using the plasmid. Similarly, claims 204-205 encompass methods of treating an allergy in a vertebrate or an allergic response to an antigen in a mammal utilizing an effective amount of an immunostimulatory nucleic acid comprising the 5'CG3' motif in any plasmid, wherein C is unmethylated, and wherein the immunostimulatory nucleic acid is

either already present in the plasmid or it is inserted into the plasmid in any desired copy numbers and an effective amount of a recombinant antigen that is produced by a process using the plasmid or as a polynucleotide encoding the antigen. The embodiments of these instant claims, claims 202-205, are not supported by the specifications of the great-grandparent application U.S. Serial No. 08/112,440, filed August 26, 1993 and the grandparent application U.S. Serial No. 08/446,691, filed June 7, 1995. There is no explicit teachings regarding to any immunostimulatory nucleic acid sequence, let alone an immunostimulatory nucleic acid comprising 5'CG3' or one comprising AACGTT in the aforementioned great-grandparent and grandparent applications. The mere mentioning that "Other preferred plasmid vectors are pREP7 and pREV which are commercially available from Invitrogen of San Diego, California" (page 23, lines 17-18 in U.S. Serial No. 08/112,440; page 33, lines 1-2, in U.S. Serial No. 08/446,691) is not an indication that at the filing dates of the great-grandparent and grandparent applications, Applicants appreciate or realize the potential usefulness of any immunostimulatory nucleic acid sequence comprising the CpG motif, wherein C is unmethylated, as an adjuvant to stimulate CTL activity or to stimulate production of interferons by lymphocytes as contemplated by the present application (page 10, first paragraph of the present specification). As such, on the basis of the aforementioned great-grandparent and grandparent applications, it is not apparent to one of ordinary skilled artisan that Applicants contemplated specifically to make and use a composition comprising a plasmid including an immunostimulatory nucleic acid sequence comprising AACGTT or 5'CG3' or introducing said immunostimulatory nucleic sequence into any

plasmid that is absent of such immunostimulatory nucleic acid sequence at any time period prior to January 30, 1996. Furthermore, there is also no support in the grandparent or the great-grandparent applications for the make and use of any plasmid containing an immunostimulatory nucleic acid sequence comprising AACGTT or 5'CG3' in conjunction or in a combination with an antigen in any form.

Accordingly, claims 202-205 are only entitled to the priority benefit of the filing date of January 30, 1996 for the reasons set forth above.

Claim 206 is entitled to the priority benefit of the filing date 8/26/1993.

Response to Arguments

In the Amendment filed on 12/9/02 in Paper No. 40, Applicants referred to the same arguments already presented in the Amendment filed on May 09, 2002 in Paper No. 35 (pages 4-5) for the issue of priority of the pending claims. Applicants' arguments have been considered and they are found to be unpersuasive for the same reasons already set forth in the Final Office Action dated 7/29/02 in Paper No. 37.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 204 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention for the same reasons set forth in the Final Office Action dated 7/29/02 in Paper No. 37.

In claim 204, the phrase "an effective amount of an immunostimulatory nucleic acid in a plasmid,....., and an effective amount of an antigen which stimulates production of allergy-associated IgE antibodies in the vertebrate, wherein said antigen is encoded in the plasmid" is unclear. A plasmid may comprise a DNA sequence coding an antigen, wherein said DNA sequence is operably linked to a promoter for the expression of an effective amount of said antigen. In Amendment C filed 10/31/01 (pages 14-15), Applicants argued that an AACGTT-containing antigen-encoding plasmid (one that is based on the vector pREP7) is a species of a composition of the presently claimed invention for claiming the priority of the great-grand parent and grandparent applications. In view of the prosecution history and in view of Applicants' arguments, Applicants appear to argue that the claim encompasses a) an effective amount of an antigen in the form of a recombinant antigen, wherein the recombinant antigen is prepared from a plasmid encoded the same, and b) an effective amount of an antigen in the form of a plasmid encoding the antigen. However as recited, an effective amount of an antigen (a protein or a peptide), which is recombinant, is not per se a nucleic acid or a cDNA contained in the plasmid. Therefore, the pending claim does not reflect Applicants' intended scope. Clarification is requested regarding whether Applicants intend to claim a method wherein an antigen is a distinct component from a plasmid containing an immunostimulatory nucleic acid comprising 5'CG3' or it is a part of said plasmid (being encoded by the plasmid). Examiner interprets the claim as a

method wherein an effective amount of a recombinant antigen which is produced by a process using a plasmid encoding the same being administered into a vertebrate to treat an allergy.

Response to Arguments

In the Amendment filed on 12/9/02 in Paper No. 40, Applicants referred to the same arguments already presented in the Amendment filed on May 09, 2002 in Paper No. 35 (page 12). Applicants' arguments have been considered and they are found to be unpersuasive for the same reasons already set forth in the Final Office Action dated 7/29/02 in Paper No. 37.

Claim Rejections - 35 USC § 102

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claim 202 remains rejected under 35 U.S.C. 102(e) as being anticipated by Davis (U.S. Patent No. 5,780,448 with the effective filing date of November 07, 1995) as

evidenced by Krieg et al. ((U.S. Patent No. 6,194,388 with the effective filing date of July 15, 1994: IDS) for the same reasons set forth in the Final Office Action dated 7/29/02 in Paper No. 37.

The claim is drawn to a composition comprising: a plasmid including an immunostimulatory nucleic acid sequence comprising AACGTT, wherein C is unmethylated, and an antigen in a pharmaceutically acceptable carrier, wherein the antigen is produced by a process using the plasmid.

Davis teaches the preparation of a composition for inducing an immune response in finfish comprising an expression vector having an expression control sequence capable of directing expression in finfish of at least one immunogenic polypeptide and a polypeptide encoding DNA sequence encoding at least one immunogenic polyeptide from a fish pathogen (an antigen), wherein the vector additionally comprises an immunostimulatory unmethylated CpG motif (see col. 4, lines 10-30; col. 11, lines 8-13 and the claims). Davis also teaches that multiple CpG motifs may be inserted into the non-coding region of the expression vector (col. 7, lines 23-25), and that expression vector includes purified plasmid DNA that is dissolved in an aqueous solution or in a formulation such as cationic liposomes, fluorocarbon emulsions, gold particles, biodegradable microspheres or cationic polymers which are pharmaceutically acceptable carriers (col. 8, lines 27-35). Davis further teach that the aforementioned pharmaceutical composition further comprising a second DNA vaccine, an adjuvant, a recombinant protein (an antigen), a transfection reagent, or some combination thereof (col. 9, lines 13-20). At the effective filing date of the present application, several

immunostimulatory nucleic acid sequences having the CpG motifs have been shown to activate the immune system, including the sequence comprising AACGTT as evidenced by the teachings of Krieg et al. (see Table 1 and the claims).

Therefore, the instant claim is anticipated by Davis as evidenced by Krieg et al.

Response to Arguments

In the Amendment filed on 12/9/02 in Paper No. 40, Applicants referred to the same arguments already presented in the Amendment filed on May 09, 2002 in Paper No. 35 (pages 12-13). Applicants' arguments have been considered and they are found to be unpersuasive for the same reasons already set forth in the Final Office Action dated 7/29/02 in Paper No. 37.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 202 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Krieg et al. (U.S. Patent No. 6,194,388 with the effective filing date of July 15, 1994: IDS) in view of Davis (U.S. Patent No. 5,780,448 with the effective filing date of November 07, 1995) for essentially the same reasons set forth in the Final Office Action dated 7/29/02 in Paper No. 37.

The claim is drawn to a composition comprising: a plasmid including an immunostimulatory nucleic acid sequence comprising AACGTT, wherein C is unmethylated, and an antigen in a pharmaceutically acceptable carrier, wherein the antigen is produced by a process using the plasmid.

Krieg et al. disclose various immunostimulatory oligonucleotides having the CpG motifs, among which is an oligonucleotide comprising AACGTT (see Table 1). For facilitating uptake into cells, the immunostimulatory oligonucleotides are preferably in the range of 8 to 40 base pairs in size (col. 6, lines 18-20). Additionally, Krieg et al. teach that the immunostimulatory oligonucleotides can be used in conjunction with a vaccine or an antigen in a pharmaceutically acceptable carrier, as an adjuvant to boost a mammal's immune response to effect better response from the vaccine (col. 17, line 65 continues to line 3 of col. 18; and the claims). Krieg et al. do not teach specifically the use of an immunostimulatory unmethylated CpG motif or an immunostimulatory

sequence comprising AACGTT in the form of a plasmid or more specifically in the plasmid pREP7 encoding an antigen.

At the effective filing date of the present application (January 30, 1996), Davis teaches that since copies of CpG motifs in DNA expression vectors act as adjuvants facilitating the induction of an immune response against an expression protein, multiple CpG motifs may be inserted into the non-coding region of an expression vector containing a sequence encoding an antigen (col. 7, lines 18-48; col. 11, lines 1-16). Davis further discloses that the antigen expressing vectors can be utilized concurrently with an antigen-based vaccine such as a recombinant protein or whole-killed vaccine (col. 8, lines 16-22). Additionally, Davis teaches that any vector can be used as an expression plasmid, and it is not limited to vectors containing constitutive promoters (e.g., Rous sarcoma virus; CMV, SV40), tissue promoters, tissue-specific promoters or promoters from the gene of the antigen being expressed (col. 6, lines 51-64).

Accordingly, it would have been obvious for one of ordinary skilled artisan to modify the composition taught by Krieg et al. by specifically incorporating one or more copies of the immunostimulatory nucleic acid sequence having the unmethylated CpG motifs, including one that comprises the sequence AACGTT taught by Krieg et al. in the non-coding region of an expression plasmid vector as taught by Davis to use it as an adjuvant for a vaccine or an antigen in a pharmaceutically acceptable carrier or for an antigen encoded in the expression plasmid vector. One of ordinary skilled artisan would have been motivated to carry out the above modification because both Krieg et al. and Davis teach that unmethylated CpG dinucleotide motifs present in plasmid vectors or in

free oligonucletides act as adjuvants to boost a mammal's immune response to effect better response from an antigen-based vaccine such as a recombinant protein or whole-killed vaccine or a plasmid DNA vaccine comprise a sequence encoding an antigen.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim 202 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Krieg et al. (U.S. Patent No. 6,194,388 with the effective filing date of July 15, 1994: IDS) in view of Applicants' admission of record (Amendment C filed 10/31/01 in Paper No. 28, page 8, second last paragraph and page 9, second paragraph) for essentially same reasons set forth in the Final Office Action dated 7/29/02 in Paper No. 37.

Krieg et al. disclose various immunostimulatory oligonucleotides having the CpG motifs, among which is an oligonucleotide comprising AACGTT (see Table 1). For facilitating uptake into cells, the immunostimulatory oligonucleotides are preferably in the range of 8 to 40 base pairs in size (col. 6, lines 18-20). Additionally, Krieg et al. teach that the immunostimulatory oligonucleotides can be used in conjunction with a vaccine or an antigen in a pharmaceutically acceptable carrier, as an adjuvant to boost a mammal's immune response to effect better response from the vaccine (col. 17, line 65 continues to line 3 of col. 18; and the claims). Krieg et al. do not teach specifically the use of an immunostimulatory unmethylated CpG motif or an immunostimulatory sequence comprising AACGTT in the form of a plasmid or more specifically in the plasmid pREP7 encoding an antigen.

However, Applicants have submitted on record that a plasmid is an obvious polynucleotide species in view of a polynucleotide of at least 8 nucleotides (the immunostimulatory oligonucleotides taught by Krieg et al. are in the range of between 2 to 100 base pairs, with a preferred embodiment between 8 to 40 base pairs in size), and that administering an antigen is obvious in view of administering an antigen encoded by a plasmid (see Amendment C in Paper No. 28; page 8, second last paragraph; page 9, second paragraph).

Accordingly, it would have been obvious for one of ordinary skilled artisan to modify the composition taught by Krieg et al. by introducing the immunostimulatory nucleic acid sequences having the unmethylated CpG motifs, including one that comprises the sequence AACGTT taught by Krieg et al. into a plasmid vector to use it as an adjuvant for a vaccine or an antigen in a pharmaceutically acceptable carrier.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

In the Amendment filed on 12/9/02 in Paper No. 40, Applicants referred to the same arguments already presented in the Amendment filed on May 09, 2002 in Paper No. 35 (page 13). Applicants' arguments have been considered and they are found to be unpersuasive for the same reasons already set forth in the Final Office Action dated 7/29/02 in Paper No. 37.

Following is a new ground of rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 204 and 205 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for suppressing an allergic response to an antigen in a mammal susceptible to an allergic reaction to said antigen which stimulates production of allergy-associated IgE antibodies in the mammal, comprising parenterally co-administering to the mammal (a) an effective amount of an immunostimulatory nucleic acid in a plasmid, said immunostimulatory nucleic acid comprising 5'CG3', wherein C is unmethylated, and (b) an effective amount of the antigen provided as the antigen *per se* or as a polynucleotide encoding the antigen;

does not reasonably provide enablement for a method of treating an allergy in any vertebrate by administering or parentally administering an effective amount of the immunostimulatory nucleic acid in a plasmid and an effective amount of the antigen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for the same reasons set forth in the previous Office Action.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction

or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

In light of the as-filed specification, as written claim 204 is directed to a method of treating an allergy in any vertebrate (e.g., frog, chicken, fish, mammal) comprising administering to the vertebrate an effective amount of an immunostimulatory nucleic acid in a plasmid, said immunostimulatory nucleic acid comprising 5'CG3', wherein C is unmethylated, and an effective amount of a recombinant antigen which stimulates production of allergy-associated IgE antibodies in the vertebrate, wherein said antigen is produced by a process using the plasmid.

Claim 205 is directed to a method for suppressing an allergic response to an antigen in a mammal susceptible to an allergic reaction to said antigen which stimulates production of allergy-associated IgE antibodies in the mammal, comprising parentally administering to the mammal: (a) an effective amount of an immunostimulatory nucleic acid in a plasmid, said immunostimulatory nucleic acid comprising 5'CG3', wherein C is unmethylated, and (b) an effective amount of the antigen provided as the antigen per se or as a polynucleotide encoding the antigen.

With respect to the nature of the instant claims, the specification teaches by exemplification showing that mice that received intradermally the pCMV-lacZ vector containing two copies of the immunostimulatory polynucleotide with the sequence AACGTT within the AmpR gene of the vector produced high titers of IgG 2A antibodies

(serological markers for a TH1 type immune response), whereas mice injected intradermally with β-galactosidase produced high titers of IgG 1 antibodies (serological markers for a TH2 type immune response). The same groups of mice were boosted with 0.5 μg of β-galactosidase intradermally, boosting intradermal pCMV-lacZ primed mice with the enzyme induced about 10-fold rise in IgG 2A antibody responses, whereas it did not stimulate an IgG 1 response. It is noted that boosting intradermal β-galactosidase primed mice with the enzyme induced a significant rise in IgG 1 responses without any stimulation of an IgG 2A response, and that boosting of intramuscular pCMV-lacZ primed mice with the enzyme has little induction in either IgG 2A or IgG 1 responses (See Figs. 15 and 16). The specification further teaches that upon an intraperitoneal challenge with β-galactosidase 14 weeks after the initial immunization, anti-β-galactosidase IgE levels in intradermal pCMV-lacZ mice were consistently low after boosting as before boosting, while protein injected mice developed high levels of anti-β-galactosidase IgE, especially after the first antigen boosting injection (Fig. 17). Furthermore, Applicants teach that CTL activity in cultures of cells from the pCMV-lacZ injected mice increased from about 18% activity to nearly 100% activity, whereas the CTL activity in cell cultures from the pKCB-lacZ (without the immunostimulatory polynucleotide) or control injected mice barely exceeded 20% lytic activity. An increase in CTL activity was however observed in cell cultures from pKCB-lacZ & pUC-19 (pUC-19 plasmid vector includes the AmpR gene) co-injected mice.

The above evidence has been noted and considered. However, the above evidence is not reasonably extrapolated to the instant broadly claimed invention for the reasons discussed below.

(a) The breadth of the claims. With respect to claim 204, the claim encompasses a method for attaining a broad range of therapeutic effects ranging from reducing or alleviating to complete abolishment or preventing symptoms associated with an allergy in a vertebrate (within the scope of treating) comprising the utilization of an effective amount of an immunostimulatory nucleic acid comprising 5'CG3' in a plasmid of the presently claimed invention. Claim 204 also encompasses any route of delivering (encompassing parenteral and mucosal routes) an effective amount of an immunostimulatory nucleic acid of the present invention into a vertebrate to treat an allergy in said vertebrate. Additionally, claim 204 encompasses a method of treating an allergy in a vertebrate including human, mouse, monkey, chicken, frog and fishes among others. Furthermore, both methods of claims 204 and 205 do not even require that an effective amount of the immunostimulatory nucleic acid in a plasmid and an effective amount of the antigen to be co-delivered parentally or otherwise in a mammal or a vertebrate for the attainment of the desired therapeutic effects contemplated by Applicants. The present specification is not enabled for such a broadly claimed invention.

(b) The amount of direction or guidance provided. With respect to claim 204 on the issue of a broad range of therapeutic effects contemplated by Applicants, there is no reasonable correlation between an apparent lack of IgG 1 response stimulation and

low levels of anti-β-galactosidase IgE levels observed in intradermal pCMV-lacZ primed mice after boosting with β-galactosidase with the prevention or abolishment of symptoms associated with any allergy in a vertebrate as encompassed by the scope of the instant claim. This is because after boosting with β-galactosidase, IgG 1 response was still present in the intradermal pCMV-lacZ primed mice, and although low levels of anti-β-galactosidase IgE were observed in the same mice, these levels are nevertheless represent a significant stimulation with respect to the pre-boosting anti-β-galactosidase IgE level (see Fig. 17). Moreover, splenocytes removed from pCMV-LacZ treated mice and challenged *in vitro* with β-galactosidase antigen are still capable of producing enhanced levels of IFN-γ and IL-4 in comparison with the splenocytes removed from the negative control pKCB-LacZ treated mice (see Example IX). The cytokine IL-4 is well known for turning on the IgE-producing cells and for development of the TH2 cells. It is also not apparent from the instant specification that an effective mucosal immunity has been established or achieved in a vertebrate by the presently claimed invention since the mucosal immunity is important to prevent pathogen entry, for this instance allergens causing allergy to yield the prophylactic or preventive therapeutic effects contemplated by Applicants.

With respect to claim 204 on the issue of any route of delivery, it is noted that even among the parenteral routes of administration, boosting of intramuscular pCMV-lacZ primed mice with the enzyme does not enhance any IgG 2A response whose level is even lower than that induced in the β-galactosidase primed mice (See Fig. 15). Boosting intramuscular pCMV-lacZ primed mice with the enzyme also does not

suppress the induction of IgG 1 response, but rather a slight stimulation was observed even though the stimulation level is much less than those obtained for intradermal pCMV-lacZ and β-galactosidase primed (See Fig. 16). Moreover, even in the absence of a subsequent boosting with the enzyme, the level of IgG 2A response to β-galactosidase is not stimulated upon intramuscular injection of pCMV-lacZ, whereas a significantly enhanced IgG 2A response was clearly observed for mice injected with β-galactosidase (see Fig. 13). Thus, it is apparent that there is a large variation in the selective induction of Th 1 response that is capable of providing the therapeutic effects contemplated by Applicants for treating an allergy between intramuscular and intradermal routes of administration, let alone any route of delivery. The instant specification offers no guidance for a skilled artisan on how to attain an induction of a desired Th1 immune response specific against an allergen or an antigen via any mucosal route, given the unpredictable state of the art for attaining a desired induction of Th1 immune response that yields therapeutic effects through the introduction of CpG containing immunostimulatory sequences into mucosal surfaces as taught by McCluskie et al. (Crit. Rev. Immunol. 19:303-329, 1999). With the lack of sufficient guidance provided by the present disclosure, it would have required undue experimentation for a skilled artisan to make and use the method as claimed.

With respect to claim 204 on the issue of treating an allergy in any vertebrate, apart from the mouse model exemplification, it is unclear whether the desired selective induction of TH1 response that is beneficial for treating an allergy could be obtained in numerous species encompassed within the broad genus of a vertebrate in the claimed

method. It is also unclear whether the immune components of a fish or a frog would react to an allergen or an antigen in a similar manner as those of a mammal, specifically an induction of allergy-associated IgE antibodies, and similarly whether an induction of the desired TH1 response would also be induced by the immunostimulatory nucleic acid of the presently claimed invention to yield the contemplated therapeutic effects. An extensive search for the prior art at the effective filing date of the present application revealed that little has been known about the immune responses in species such as frog, fish or chicken, let alone on the preferential induction in TH1 immune response for treating allergy in these species. As such, the contemplated therapeutic results for a broad number species encompassed by the scope of the present application would not be predictive. Thus, with the lack of sufficient guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make and use the method as claimed. Furthermore, regarding to the breadth for treating an allergy in any vertebrate in the method as claimed, Applicants' attention is further directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Additionally, the courts have also stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in the patent application (27 USPQ2d 1662 *Ex parte Maizel.*).

With respect to the issue that there is no requirement that both the immunostimulatory nucleic acid in a plasmid and the antigen to be co-delivered into a vertebrate or a mammal in order to attain the desired therapeutic effects as encompassed by the claimed methods, the instant specification fails to provide any guidance (e.g., any example) for a skilled artisan on how to attain such contemplated therapeutic effects when the immunostimulatory nucleic acid and the antigen are administered separately. The exemplifications only show the delivery of a vector containing two copies of the immunostimulatory polynucleotide and a nucleotide sequence encoding an antigen (β-galactosidase) in the mouse model. It should be noted that the physiological art is recognized as unpredictable (MPEP 2164.03). Therefore, with the lack of sufficient guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make and use the methods as claimed.

(c) The state of the prior art and the unpredictability of the prior art. Even several years after the effective filing date of the present application, the role of CpG immunostimulatory sequence in regulating host immune responses is still not clearly understood as exemplified by the teachings of McCluskie et al. (Crit. Rev. Immunol. 19:303-329, 1999). McCluskie et al. stated that "[I]t is possible that the CpG content of the vector may influence whether immune responses are biased towards a Th1- or Th2-type and explain, at least in part, why different plasmids induce predominantly Th1, Th2, or mixed Th1/Th2 responses when naked DNA is delivered to the lungs" (page 313, col. 2, first paragraph). McCluskie et al. further noted that various other factors such as the

antigen, the dose of antigen, the route and method of DNA administration, the coexpression of cytokines and the presence or absence of other adjuvant may also involve in determining whether a Th1 or Th2 response predominates after mucosal immunization. As such, it is uncertain whether the broad scope of therapeutic effects contemplated by Applicants could be obtained by a skilled artisan without undue experimentation.

As already stated above, an extensive search for the prior art at the effective filing date of the present application revealed that little has been known about the immune responses in species such as frog, fish or chicken, let alone on the preferential induction in TH1 immune response useful for treating allergy (e.g., suppression of allergy-associated IgE antibodies) in these species. As such, the contemplated therapeutic results for a broad number species encompassed by the scope of the present application would not be predictive, and since the physiological art is recognized as unpredictable (MPEP 2164.03).

Several years after the effective filing date of the present application, Caufield (WO 98/52962; IDS) has shown that injection of a CpG containing oligonucleotide in the opposite leg from the antigen did not result in an adjuvant effect, indicating that certain CpG containing oligonucleotides do not simply increase innate immunity, rather they elicits a localized adjuvant effect at the site of injection or, possibly, in the draining lymph node (see example 5 on pages 25-26). Therefore, it is unclear from this disclosure whether in the absence of a co-administration of CpG containing immunostimulatory nucleic acid and the antigen into a vertebrate or a mammal, would

an effective immune response be induced to yield the therapeutic effects contemplated by Applicants. Again, with the lack of sufficient guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make and use the methods as claimed.

Accordingly, due to the lack of guidance provided by the specification regarding to the issues set forth above, the unpredictability of the physiological art and DNA vaccination, coupled with the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Response to Arguments

In the Amendment filed on 12/9/02 in Paper No. 40, Applicants referred to the same arguments already presented in the Amendment filed on May 09, 2002 in Paper No. 35 (pages 6-12) for some of the enablement issues raised for claim 204. Applicants' arguments have been considered and they are found to be unpersuasive for the same reasons already set forth in the Final Office Action dated 7/29/02 in Paper No. 37.

Claims 203 and 206 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 203 is drawn to a composition comprising a plasmid including an immunostimulatory nucleic acid sequence comprising AACGTT, wherein C is methylated, and an antigen in a pharmaceutically acceptable carrier, wherein the antigen is encoded in the plasmid, and wherein the plasmid is pREP7 encoding an antigen.

Claim 206 is directed to a pharmaceutical composition for stimulating an immune response to an antigen, comprising pREP7 encoding the antigen and a pharmaceutically acceptable carrier.

The specification is not enabled for the instant claimed invention because it fails to provide a deposit for the pREP7 encoding an antigen, which is an essential component for the pharmaceutical compositions as claimed. Since the cloning vector pREP7 is a discontinued product from Invitrogen, and therefore it is no longer publicly available to the public, it is incumbent upon the instant specification to provide sufficient guidance for a skilled artisan on how to make the pREP7 vector encoding an antigen for the pharmaceutical compositions as claimed. In the absence of such guidance, it would have required undue experimentation for one skilled in the art to make and use the instant invention. The requirements of 35 USC 112 may be satisfied by a deposit of the pREP7 encoding an antigen plasmid. 37 CFR 1.802. The specification does not disclose a repeatable process on how to obtain the plasmid. Thus, a deposit is required for enablement purpose. If the deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the plasmid has been

deposited under the Budapest Treaty and that the plasmid will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. 37 CFR 1.808.

If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.808, applicants may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;
(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;
(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;
(d) a viability statement in accordance with the provisions of 37 CFR 1,807; and
(e) the deposit will be replaced if it should ever become nonviable.

Accordingly, due to the issue discussed above, it would have required undue experimentation for one skilled in the art to make and use the presently claimed invention.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (703) 308-1906, or SPE, Irem Yucel, Ph.D., at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to LIE, Zeta Adams, whose telephone number is (703) 305-3291.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER